REMARKS

Claims 1-3 and 31 are pending.

Claim 1 has been amended. Support for the amendments to claim 1 can be found, for example, in the Specification at page 17, lines 7-19 ("obtaining a sample from a test subject, said sample containing eosinophil cells"); page 53, lines 3-12 ("measuring the expression level of a gene or genes encoding TR3, TINUR or TR3 and TINUR"); and page 4, lines 24-27, page 13, lines 18-20, and Table 7 and page 53, lines 17-19 ("determining whether the expression level of the gene or genes in the sample is elevated compared to the expression level of the gene or genes in the eosinophil cells of normal subjects").

No new matter has been added.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3 and 31 are rejected under 35 U.S.C. § 112, first paragraph as lacking enablement for the method of testing for an allergic disease. The Examiner states that Applicants are enabled for diagnosing atopic dermatitis by the recited methods. However, the Examiner further states that Applicants are not enabled for diagnosing all allergic diseases by the recited methods as the specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate with these claims. Specifically, the Examiner states that, "[d]ue to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activation of these two genes in all forms of allergic disease, the lack of direction/guidance presented in the specification regarding which structural features are required to promote activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of constitutive activation of these transcription factors in numerous cell lines, and the breadth of the claims which fail to recite any limitations of allergic disease, other than atopic dermatitis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention for all allergic diseases." (Office Action at page 4, lines 6-14).

Legal Standard and General Remarks

The claims are enabled if the person of skill in the art could make and use the claimed invention without undue experimentation. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 1404. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id. Not everything necessary to practice the invention need be disclosed, and what is well-known is preferably omitted from the specification. In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The scope of enablement must only bear a reasonable correlation to the scope of the claims. In re Fischer, 166 USPQ 18, 24 (CCPA 1970). (See also, MPEP § 2164.08 at 2100-205 (8th Ed., Rev. 3, Aug. 2005)).

Factors to be considered in determining if an invention is enabled include (1) the nature of the claimed invention, (2) the breadth of the claims, (3) the relative skill in the art, (4) the state of the prior art, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary to make or use the invention, (7) the amount of direction or guidance presented in the application, and (8) the predictability or unpredictability of the art. Wands, 8 USPQ2d at 1404. No one factor is determinative. However, the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed methods using the teachings and guidance of the application, and his knowledge and skill in the art, without undue experimentation.

Nature of the claimed invention and breadth of the claims.

Claim 1 has been amended to better define the claimed method. Thus, the claims are drawn to a method of testing for an allergic disease by measuring the expression level of a gene or genes encoding TR3, TINUR or TR3 and TINUR in the eosinophil cells of a test subject and determining whether the level of expression of the gene or genes measured is elevated compared to the level of expression of the gene or genes in the eosinophil cells of those not having an allergic disease (e.g., normal subjects). If the expression level of the gene or genes is elevated

compared to the expression of the same gene or genes in normal subjects, this indicates that the test subject has an allergic disease.

The claimed method is a diagnostic (and not a therapeutic) method to be carried out on a sample from a subject. The claims' breadth is limited to determination of the expression level of just two genes (TR3 and/or TINUR) in one particular cell type (eosinophil cells). The claims are directed to testing for allergic diseases in general; however, the specific involvement of eosinophil cells in allergic diseases was well-established in the art at the time the application was filed. Thus, one having skill in the art would have been able to practice the claimed method based on his knowledge in the art regarding the link of eosinophil cells to all allergic diseases.

The relative skill in the art and the state of the prior art.

The relative skill in the art at the time the application was filed was high. It was routine for one skilled in the art to perform the steps recited in the method, that is: obtain a sample of eosinophil cells from a subject, measure the expression level of the TR3 and/or TINUR gene in those cells and determine whether the level of expression measured is elevated compared to a baseline level of expression of those genes found in subjects without an allergic disease. At the time the application was filed, techniques for recovering a sample of eosinophil cells from a subject were known (see Hansel TT *et al.*, *J Immunol Methods* 145(1-2):105-110, 1991; Nutku E *et al.*, *J Immunol* 167(2):1039-1046, 2001; Thomas LL *et al.*, *J Immunol* 169(2):993-999, 2002). Similarly, numerous suitable techniques for measuring the expression level of a gene in a cell were well-known to the skilled artisan at the time (see Sambrook *et al.*,1989, Molecular Cloning: A Laboratory Manual, Second Ed., Book 2, Chapters 9-11 and 13-14, Cold Spring Harbor Laboratory Press and Ausubel FM *et al.* (eds.), 1998 Current Protocols in Molecular Biology, Chapters 2 and 4, John Wiley & Sons, NY). In addition, methods to determine whether the expression level of a gene of interest was higher than the expression level of that same gene in an appropriate control were not only well-known, but performed routinely, being an essential element of experiments of this type undertaken in the art.

Moreover, at the time the application was filed, allergic diseases were known to be characterized by an increased number of eosinophil cells and/or an increase in their activity. As noted previously (see Amendment of record, filed May 26, 2005), it was well-established that

eosinophils were prominent at sites of allergic reactions and that they played a central role in all allergic diseases, mediating inflammatory and cytotoxic events associated with allergic disorders. (See Gleich GJ *et al.*, 1993, *Annu Rev Med* 44:85-101; Krogel C *et al.*, 1994, *Eur Respir J* 7:743-760; Howarth PH *et al.*, 2000, *Allergy* 55:7-16,; Weller PF 1994, *Curr Opinion Immunol* 6:85-90). In fact, the increase in and activation of eosinophil cells were used as a marker of allergic reaction, as an increase in their numbers were known by those having skill in the art to be correlated with disease severity (see Bochner *et al.*, *Annu Rev Immunol*, 12:295-335, 1994; Lukacs *et al.*, *Am J Respir Cell Mol Biol* 13(1):1-6, 1995; Resnick MB and Weller PR, *Am J Respir Cell Mol Biol* 8(4):349-355) and their activation was known to perpetuate inflammation (see Weller PF, *N Engl J Med* 324:1110-1118, 1991 and Kay AB, *J Allergy Clin Immunol* 87:893-910, 1991).

Accordingly, based on the teachings of the aforementioned references, it is clear that a person having ordinary skill in the art at the time the application was filed knew that eosinophil cells were intimately linked to and served as mediators of *all* allergic diseases, knowledge that led to the presence and/or activation of eosinophils to be used as typical clinical indicators of allergic diseases in general.

The presence of working examples.

The Specification discloses and exemplifies a method to identify genes with changed (e.g., elevated) expression in the eosinophil cells of subjects with various severities of an allergic disease (i.e, atopic dermatitis) compared to the expression of these same genes in subjects without allergic disease (i.e., healthy and/or normal subjects). (See Example 1). Moreover, the Specification discloses and exemplifies methods to measure the expression level of the genes identified as having eleveated expression, TR3 and TINUR. Thus, the Specification discloses and exemplifies procedures to isolate eosinophils from a subject (see at page 37, line 20-page 38, line 8), extract RNA from the isolated eosinophil cells (see at page 38, lines 9-18), produce cDNA from the RNA extracted from the eosinophil cells (see at page 38, lines 22-36), perform polymerase chain reaction (PCR) to ascertain the expression level of the genes in the eosinophil cells of a subject with an allergic disease (i.e., atopic dermatitis) and the expression level of the genes in subjects without an allergic disease (i.e., healthy or normal subjects) (see at page 40, line

15-page 42, line 5 and at page 53, lines 12-16) and perform a statistical analysis of the gene expression data to determine the significance of the changes in expression of the genes in subjects with allergic disease (see at page 46, lines 1-14).

The exemplifications described above are adequate to enable one with skill in the art to practice the claimed invention.

The amount of direction or guidance presented in the application and the quantity of experimentation necessary to make or use the invention.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance in the Specification using his knowledge in the art with no more than routine experimentation. Methods suitable for measuring the expression level of a gene (e.g., TR3 or TINUR) from a specified cell and determining if the expression level measured is elevated compared to that in a particular control were well-known in the art at the time the application was filed. In addition, the Specification provides extensive guidance on practicing the claimed invention including: how to obtain from a subject being tested a sample containing eosinophil cells (see at page 17, lines 7-16 and Example 1), what constitutes a gene that encodes TR3 and TINUR (see at page 12, lines 18-27), how to measure the expression level of TR3 and/or TINUR in the eosinophil cells in a sample and how to visualize and quantify the expression level of the genes (see at page 14, line 3-page 16, line 6) in order to determine whether their expression level in the eosinophil cells of the test subject is elevated compared to that in subjects without allergic disease, a finding that would be indicative of allergic disease in the subject being tested.

Further, it was well-known in the art that an increase in the number of and the activation of eosinophils characterized all allergic diseases and that eosinophils constituted major effector cells in inflammatory processes underlying the pathogenesis of allergic disease. Moreover, the Specification reiterates/teaches (see at page 2, lines 29-34) that which was known to the person of skill in the art- that eosinophils "are clinically important as diagnostic markers and a guide to the management of allergic disease"(see abstract, Wardlaw *et al.*, *British Medical Bulletin* 56:985-1003, 2000). Consequently, the skilled artisan would have concluded that the results disclosed and exemplified in the Specification, that is, results demonstrating elevated expression

of TR3 and TINUR in the eosinophil cells of subjects with atopic dermatitis, could be applied to any other allergic disease and thus, doing no more than routine experimentation, could practice the claimed invention. Accordingly, based on the disclosure in the Specification and his knowledge, the skilled artisan could make and use the claimed invention (i.e., a method to detect elevated expression of TR3 and/or TINUR in the eosinophil cells of a subject in order to test for an allergic disease) to diagnose any allergic disease without undue experimentation.

The predictability or unpredictability of the art.

As discussed previously, it was known in the art at the time the application was filed that eosinophil cells were associated with and instrumental in allergic diseases in general. Further, information known in the art would indicate to one having skill in the art that the results exemplified in the application relating to atopic dermatitis could be extrapolated to all allergic diseases with predictable results. For example, corticosteroids, the most commonly used class of medications to treat allergic disease were known in the art to be effective due to their ability to target eosinophils, the drugs decreasing eosinophil chemotaxis, activation and inflammatory cytokine production and reducing their number. At the time of the invention, corticosteriods were used to treat a number of allergic diseases including asthma, atopic dermatitis, eosinophilic arthritis and eosinophilic cystitis. (See Barnes PJ, *N Engl J Med* 332(13):868-875, 1995; Tay C-H, *Rheumatology* 38(12):1188-1194, 1999; Verhagen PCMS *et al.*, *Arch Dis Child* 84:344-346, 2001). Based on the knowledge of the skilled artisan that corticosteriods, by inhibiting eosinophils, were used to effectively treat a number of allergic diseases, one having skill in the art would conclude that a diagnostic method for allergic disease, based on the presence of eosinophil cells could, similarly, be used to identify any allergic disease.

Thus, with the known predictability of eosinophil presence and activity in all allergic diseases, one skilled in the art would expect that a gene or genes (i.e., TR3 and TINUR) found to have an expression level that increases in eosinophil cells known to be present and active in a representative allergic disease (i.e., atopic dermatitis) could be used as an index to practice the claimed method to detect any allergic disease. In other words, it would be reasonable for one skilled in the art, using his knowledge of the art and its predictability, to extrapolate the disclosed results over the full scope of the claimed invention. It is not necessary to perform a comparative

experiment for every possible permutation of the claimed invention and prior art when the results already presented can be reasonably extrapolated to the full scope of the claims. *In re Kollman*, 201 U.S.P.Q. 193 (C.C.P.A. 1979). In this case, one having skill in the art would conclude that the scope of enablement clearly bears a reasonable correlation to the scope of the claims.

Further, at the time the application was filed, the skill in the art was high with regard to measuring and comparing the expression level of a gene, as evidenced by the numerous techniques for doing so disclosed in the Specification (see at page 14, line 3-page 16, line 6) and in the literature of the art in general (Sambrook *et al.*,1989, Molecular Cloning: A Laboratory Manual, Second Ed., Book 2, Chapters 9-11 and 13-14, Cold Spring Harbor Laboratory Press and Ausubel FM *et al.* (eds.), 1998 Current Protocols in Molecular Biology, Chapters 2 and 4, John Wiley & Sons, NY). Thus, there is no element of the claimed method whose practice would have been unpredictable to the skilled artisan at the time the application was filed.

Therefore, in view of the knowledge in the art regarding the association between eosinophils and allergic disease, the Specification fully enables the claims such that one having skill in the art could make and use the invention with an anticipation of success.

In view of the foregoing the application satisfies the enablement requirement, as any person skilled in the art at the time the application was filed could have practiced the claimed invention by following the teachings, guidance and examples of the application, using his knowledge of the art, without undue experimentation. As discussed above, it was well-known in the art that eosinophils were inextricably linked to allergic disease:

> "Eosinophils are the hallmark of allergic inflammation. In allergic diseases, eosinophil numbers correlate with disease severity."

(Nutku E *et al.*, *J Immunol* 167(2):1039-1046, 2001, at page 1039, col. 1)
Applicants' disclose and exemplify elevated expression of the genes TR3 and TINUR in the eosinophil cells of those having atopic dermatitis, a representative allergic disease, that, like other allergic diseases, was known to those having skill in the art to be characterized by an increase in eosinophil cell number and activity. Because eosinophil cells are a feature of all allergic diseases, Applicants' findings in atopic dermatitis can be extrapolated to all allergic

diseases. Thus, if Applicants' are "enabled for diagnosing atopic dermatitis using the claimed method" (Office Action at page 2, lines 26-27), then they are enabled for diagnosing any allergic disease by the claimed method. Moreover, as the skilled artisan is able to practice the claimed invention based on his knowledge of and skill in the art without undue experimentation, the courts have made it clear that Applicants should not be limited to claiming only that which they have exemplified. In *In re Goffe*, the Federal Circuit Court stated:

> "[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."

(*In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).

The Examiner has alleged that, for a variety of reasons, the claims are not fully enabled by the Specification, many of the reasons related to that which is unknown about TR3 and TINUR function and regulation. (See Office Action, 6., at page 2, line 24-page 4, line 20). Knowledge or understanding of the function, activity, activation, regulation, ligands and/or binding partners of TR3 or TINUR is irrelevant to the practice of the claimed invention, which simply uses the elevated expression of the genes as a marker/index of allergic disease. One need not know how or why the expression of TR3 or TINUR is elevated, nor the effects of that increased expression on eosinophil cells or allergic disease; one need only know that their expression is elevated. All that is necessary for one having skill in the art to practice the claimed invention is his knowledge of the art (e.g., that regarding the presence and/or participation of eosinophil cells in all forms of allergic disease) and that which is disclosed and exemplified in the application specification: how to obtain a sample of eosinophil cells from a subject being tested, measure the expression level of TR3 and/or TINUR in those cells and compare that expression level to the expression level of TR3 and/or TINUR found in subjects not having allergic disease and, in that way, determine if the subject being tested has an allergic disease. No more is required.

Accordingly, claims 1-3 and 31 fulfill the requirements of 35 U.S.C. § 112, first paragraph pertaining to enablement. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 103(a)

Claims 1-3 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakajima T. *et al.*, *Blood* 98(4):1127-1134 (2001). The Examiner states that Nakajima *et al.* teaches a method of testing gene expression levels in eosinophils, including gene expresssion levels in patients with atopic dermatitis utilizing a high density oligonucleotide expression probe array and that Nakajima *et al.* teaches gene expression analysis by RT-PCR in the confirmation of oligonucleotide gene expression results. The Examiner notes that Nakajima *et al.* does not teach increased expression levels of TR3 or TINUR. However, the Examiner states that it would have been obvious to a person of ordinary skill in the art at the time the application was made to determine the expression levels of TR3 or TINUR in eosinophils because "both TR3 and TINUR genes were present on the AFFYMETRIX U95A chipset used by Nakajima *et al.*" and that "the skilled artisan would have only had to look at the data to determine whether the expression levels of TR3 and TINUR were increased or decreased over controls in atopic dermatitis." (Office Action at page 5, lines 24-28).

Legal Standard and General Remarks

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Importantly, the initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious

subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). (See also MPEP § 2142, at 2100-134, col. 1, 8th Ed. (Rev. 3, Aug. 2005)).

The mere fact that a reference can be modified does not render the resulting modification "obvious" unless the prior art also suggests the desirability of the modification. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Similarly, although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432. In other words, a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" is not sufficient to establish a *prima facie* case of obviousness without some objective reason to modify or combine the teachings of the reference(s). *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000). (See also MPEP § 2134.01, at 2100-137, col. 1-2, 8th Ed. (Rev. 3, Aug., 2005)).

The Examiner has not established a prima facie case of obviousness. As note above (see *Legal Standard and General Remarks*), the mere fact that the prior art system is "capable of" performing the claimed method is not dispositive of the issue of obviousness. Nakajima *et al.* does not explicitly, implicitly or inherently suggest the claimed invention of the instant application. Specifically, there is no guidance in the Nakajima reference directing one skilled in the art to take note of the expression levels of TINUR or TR3, two of 12,000 genes measured by the GENECHIP, much less correlate any elevated expression level measured with allergic disease. In other words, the mere fact that the raw data was "available" and "could" have been interpreted in accordance with Applicants' invention does not render obvious the actual performance of the interpretation steps recited in amended claim 1, namely- determining whether the expression level of the gene or genes encoding TR3, TINUR or TR3 and TINUR is elevated in the eosinophil cells of a test subject compared to the expression level of the same gene or genes in the eosinophil cells of normal subjects, wherein the determination that the expression

level of the gene or genes in the sample is elevated indicates that the test subject has an allergic disease.

Moreover, the goal of the Nakajima *et al.* reference was to identify cell-type-specific transcripts, i.e., transcripts specific to either mast cells or eosinophils, respectively, as compared to other leukocytes. To that end, Nakajimi *et al.* identifies the top 30 eosinophil-specific transcripts using samples from healthy patients (see Table 2). Nakajima *et al.* next used the GENECHIP to "measure major granule proteins in eosinophils derived from 6 patients with atopic dermatitis." (See at page 1131, col. 1, para. 4). When comparing the expression levels of the transcripts set forth in Table 2 between healthy and allergic samples, they noted that the expression levels of Charcot-Leyden crystal protein, eosinophil derived neurotoxin, eosinophil cationic protein and MBP were relatively higher in the atopic dermatitis samples. Thus, the only comparison step suggested by Nakajima *et al.* involved comparing the expression levels of major granule proteins such as Charcot-Leyden crystal protein, eosinophil derived neurotoxin, eosinophil cationic protein and MBP. Nakajima *et al.* did not identify TR3 or TINUR as one of the transcripts notably upregulated under their experimental conditions, nor was there any suggestion or motivation in the reference to consider and/or evaluate the expression levels TR3, TINUR or any of the other remaining 11,970 genes on the GENECHIP. Despite the Examiner's assertion that "the skilled artisan would have only to look at the data to determine whether the expression levels of TR3 and TINUR were increased or decreased over controls in atopic dermatitis," the fact remains that the authors of Nakajima *et al.* actually failed to look for such a variable expression and, given the aim of the study (i.e., to identify cell-type specific transcripts), neither they, nor any one skilled in the art viewing the results, would have been motivated to do so. Thus, the modification proposed by the Examiner can only be attributed to improper hindsight reconstruction based on Applicants' disclosure.

Accordingly, given the lack of suggestion, teaching and motivation for one having skill in the art to analyze and/or modify the results of Nakajima *et al.* to arrive at Applicants' invention, Applicants' claimed invention can not be obvious in view of Nakajima *et al.* Consequently, Applicants' claimed invention is patentable over Nakajima *et al.*, claims 1-3 and 31 meeting the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are requested.

Information Disclosure Statement

As requested by the Examiner, Applicants are submitting a clean copy of the IDS submitted on 6/17/2004 so that the Examiner can sign and indicate that references AM, AO and AQ have been fully considered.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Kamilah Alexander

Kamilah Alexander
Registration No. 57,210
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: February 3, 2006